PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

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PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	23 MAY 2005
Applicant's or agent's file reference EX04-059C-PC	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US04/26231	12 August 2004 (12.08.2004)	13 August 2003 (13.08.2003)

International Patent Classification (IPC) or both national classification and IPC

IPC(7): G01N 33/53 and US Cl.: 435/7.1

Applicant

EXELIXIS, INC.

1. This opinion contains indications relating to the following items:

- [x] Box No. I Basis of the opinion
- [ ] Box No. II Priority
- [ ] Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- [ ] Box No. IV Lack of unity of invention
- [x] Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- [ ] Box No. VI Certain documents cited
- [ ] Box No. VII Certain defects in the international application
- [ ] Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis(b)* that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US04/26231

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language _____, which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material

      ☒ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material

      ☒ in written format

      ☒ in computer readable form

   c. time of filing/furnishing

      ☒ contained in international application as filed.

      ☒ filed together with the international application in computer readable form.

      ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US04/26231

Box No. V Reasoned statement under Rule 43 *bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims 1-25	YES
	Claims NONE	NO
Inventive step (IS)	Claims 1-25	YES
	Claims NONE	NO
Industrial applicability (IA)	Claims 1-25	YES
	Claims NONE	NO

2. Citations and explanations:

Claims 1-25 meet the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest that the MELK polypeptide is involved in the RAC pathway, thus discover the role of MELK protein in the modulation of the RAC pathway is novel. Accordingly, use of screening method to identify any compound capable of modulating the RAC by interacting with the MELK polypeptide meets criteria of novelty and inventive step outlined by the Rule PCT article 33(2)-(3).

Furthermore, prior arts, such as Heyer et al. (Development Dynamics 1999 Vol. 215, pages 344) merely disclose that MELK gene's isolation and characterization. Heyer et al. merely teach that the MELK expression in different stages of development, including maturation of oocytes, and preimplantation development (See whole document). At most, Heyer et al. surmise that MELK may play a role during preimplantation embryonic development (See discussion). Therefore, application of the RAC modulating agents which are capable of binding to the MELK, to restore defective RAC cell, or diagnosis of the a patient using the MELK expression is also considered novel, albeit whether any solid concrete evidence of the link on MELK with the disease has been established remains to be determined.

Claims 1-25 meet the criteria set out in PCT Article 33(4), and thus the current application possesses industrial applicability because the subject matter claimed can be made or used in basic research field, such as identifying candidate drug, or compounds capable of modulating RAC signal pathway specifically bind to a particular protein, namely maternal embryonic leucine zipper kinase (MELK). Additionally, the current invention can also be used to clinical diagnosis. For example, the instant invention can be used to detect the presence of the MELK specific antibody by isolating patient's serum, presumably containing the MELK's antibody, then interact with the MELK probe for determining the presence of the MELK associated disease.